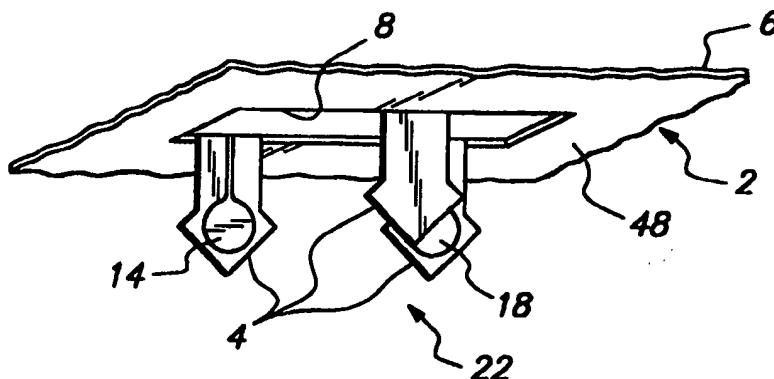




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| (21) International Application Number: PCT/US98/06851 (22) International Filing Date: 3 April 1998 (03.04.98) (30) Priority Data: 60/043,851 11 April 1997 (11.04.97) US (71) Applicant (for all designated States except US): ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DADDONA, Peter, E. [US/US]; 35 Anderson Way, Menlo Park, CA 94025 (US). FIELDSON, Gregory, T. [US/US]; P.O. Box 855, Palo Alto, CA 94302-0855 (US). NAT, Avtar, S. [US/US]; 34131 Siward Drive, Fremont, CA 94555-2128 (US). LIN, Wei-Qi [CN/US]; 72 Peter Coutts Circle, Palo Alto, CA 94305 (US). (74) Agents: MILLER, D., Byron et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). | | (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> |
| (54) Title: MINIMALLY INVASIVE DETECTING DEVICE (57) Abstract An agent detecting device comprising a plate (6) having a plurality of microprotrusions (4) for piercing the skin of a patient. Each of the microprotrusions (4) having an electrode (14, 16 and 18) thereon for detecting the presence of an agent in the patient's interstitial fluid. | | |



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MINIMALLY INVASIVE DETECTING DEVICE

TECHNICAL FIELD

The present invention relates to percutaneous detecting devices. More particularly, this invention relates to percutaneous detecting of agents, such as body electrolytes, glucose, alcohol, pharmaceuticals and illicit drugs using transcutaneous sensors.

BACKGROUND ART

Interest in the percutaneous detecting of body analytes (i.e., fluid electrolytes), organics (e.g., glucose), pharmaceuticals and illicit drugs has grown over the years. In recent years, a number of electrochemical sensors have been developed for detecting each of these analytes in the blood or interstitial fluid of a patient. For example, glucose sensors have been developed for obtaining an indication of blood glucose levels in diabetic patients. Existing electrochemical sensors require either collection of a sample from the patient or some form of invasive insertion of a sensor probe into the patient.

Thin film electrochemical sensors have been developed for subcutaneous placement of sensor probes in direct contact with the patient's blood or other extracellular fluid. One such example of a thin film electrochemical sensor, disclosed in U.S. Patent No. 5,391,250 issued to Cheney, II et al., is fabricated using thin film mask techniques. With thin film mask techniques, three thin film conductive elements are laid down in close parallel relation on a substrate and encased between flexible insulating layers of polyimide material. The conductive elements are left exposed at the distal end of the electrochemical sensor for placement in direct contact with the patient's blood. Appropriate electrode chemistries are applied to the exposed conductive elements for use as a blood glucose sensor. One of the exposed conductive elements has a coating containing glucose oxidase to define a working electrode. The other two exposed conductive elements are coated with other suitable materials or left uncoated to define a reference electrode and a counter electrode for the electrochemical sensor. The conductive elements are left exposed at the externally located proximal end for connection to a suitable monitor.

The exposed conductive elements at the distal end of the electrochemical sensor are transcutaneously placed using a sensor insertion set such as disclosed in U.S. Patent No. 5,390,671 issued to Lord et al. The sensor insertion set comprises a separate slotted insertion needle extending through a mounting base that attaches onto the patient's skin. The thin film sensor has a proximal end carried by the mounting base and a distal segment with the exposed sensor electrodes thereon protruding from the mounting base. The proximal end of the sensor is linearly offset from the distal segment so that the distal segment can be fitted into the slotted insertion needle while the proximal end is carried by the mounting base. The distal segment is transcutaneously placed as the insertion needle pierces the patient's skin upon the mounting base being pressed onto the patient's skin. The insertion needle is then withdrawn over the electrode from the patient leaving the distal segment at the selected site and the mounting base on the patient's skin.

16 Insertion of the needle is comparatively invasive, painful and
17 frightening to many patients. Therefore, there is a need for a minimally
18 invasive, painless placement of electrochemical sensors in the patient's skin.
19 Furthermore, it is desirable in some circumstances to apply the
20 electrochemical sensors to individual skin-piercing elements rather than in
21 close parallel relation on one sensor probe for improved manufacturability.

DESCRIPTION OF THE INVENTION

25 The present invention is a detecting device and method for placing an
26 electrochemical sensor in contact with a patient's interstitial fluid with skin
27 piercing microprotrusions in a minimally invasive manner. The device of the
28 present invention pierces the stratum corneum of a body surface to position
29 the electrochemical sensor just below the outermost layer of the epidermis
30 but above the patient's nerve endings and blood vessels to eliminate pain and
31 bleeding for the patient. The present invention integrates an electrochemical
32 sensor and at least one skin-piercing member into one device to achieve in
33 situ detection with a painless application.

In one aspect, the invention comprises a plurality of microprotrusions for piercing the skin in which each microprotrusion forms an individual electrode of an electrochemical sensor, instead of all of the electrodes on one probe, to maximize the electrode area while maintaining the small protrusion

1 size necessary for minimally invasive operation. In another aspect, the
2 electrodes are coated onto each side of the microprotrusions to increase the
3 active electrode area.

4 In another aspect of the invention, the device utilizes a member having
5 an opening therethrough in communication with a fluid-attracting member, a
6 plurality of microprotrusions extending downward from a first side of the
7 member, and a thin-film electrode on the microprotrusions which form an
8 electrochemical sensor. With the thin-film electrodes inserted in the patient's
9 skin, a constant flow of interstitial fluid past the electrodes can be maintained
10 by drawing the fluid through the opening with the fluid-attracting member
11 (e.g., an osmotic salt layer).

12 BRIEF DESCRIPTION OF THE DRAWINGS

13
14
15 Figure 1 is a top plan view of a portion of a member with
16 microprotrusions having sensor electrodes thereon;

17 Figure 2 is a bottom perspective view of the member of Figure 1 after
18 the microprotrusions have been bent into position;

19 Figure 3 is an enlarged partial cross-sectional view of a detecting
20 device in accordance with the present invention;

21 Figure 4 is an enlarged perspective view of the bottom side of a
22 member in accordance with another embodiment of the present invention;
23 and

24 Figure 5 is a diagrammatic cross-sectional view of an osmotic
25 detecting device in accordance with the present invention.

26 27 MODES FOR CARRYING OUT THE INVENTION

28
29
30 Turning now to the drawings in detail, one embodiment of the skin
31 piercing member 2 of the present invention is generally shown in FIGS. 1 and
32 2. Member 2 is used for the percutaneous detecting of an agent. The term
33 "detecting" is used broadly herein to include detection of or sensing the
34 presence or amount of an agent, as well as monitoring the presence or
35 amount of an agent. The terms "substance", "agent" and "drug" are used
36 interchangeably herein and broadly include substances such as glucose,

1 body electrolytes, alcohol, illicit drugs, pharmaceuticals, etc. that can be
2 sampled through the skin. The major barrier properties of the skin, such as
3 resistance to agent detecting, reside with the outer most layer (i.e., stratum
4 corneum). The inner division of the epidermis generally comprises three
5 layers commonly identified as stratum granulosum, stratum malpighii, and
6 stratum germinativum. There is essentially little or no resistance to movement
7 of an agent through the stratum granulosum, stratum malpighii, and stratum
8 germinativum. The device of the present invention is used to pierce the
9 stratum corneum 24 for in situ detecting of an agent with a sensor located
10 below the outermost layer of the patient's skin (FIG. 3).

11 Member 2 comprises a plurality of microprotrusions 4 which are sized
12 and shaped for piercing the outermost stratum corneum layer of (e.g., human
13 or other animal) skin. FIG. 1 shows the microprotrusions 4 after they are
14 formed (by a photolithography process followed by a chemical etching
15 process described in more detail hereinafter) and after coating (e.g., by
16 printing) electrodes 14, 16, 18 and electrical traces 20 thereon. FIG. 2 shows
17 the microprotrusions 4 after they have been bent to extend (e.g.,
18 perpendicularly) downward from the plane of plate 6. FIG. 4 shows member
19 2 in an inverted position to better show the microprotrusions 4. Only a portion
20 of the plate 6 is shown in FIGS. 1, 2 and 4. The member 2 provides for the
21 transcutaneous placement of a flexible sensor 22 having one or more
22 electrodes at a selected site within the body of a patient. Particularly member
23 2 facilitates the placement of a flexible thin film electrochemical sensor of the
24 type used for detecting specific parameters representative of patient
25 conditions. Placing the sensor within the skin of the patient allows in situ
26 readings to be obtained instead of relying on collecting interstitial fluid into an
27 absorbing member. The in situ detection minimizes lag time in the readings
28 compared to diagnostic methods which rely on extracting the interstitial fluid
29 before the measurement can take place. In one preferred embodiment, the
30 sensor is designed to monitor glucose levels in diabetic patients.

1 In the embodiment illustrated in FIGS. 1 and 2, the member 2
2 comprises a three electrode electrochemical sensor shown generally at 22
3 having a sample electrode 14, common electrode 16 and reference electrode
4 18. Electrical traces 20 are routed from each electrode along the upper
5 surface of the device 2 for interface with an electronic control unit or detector
6 10 (shown schematically in FIG. 3). The three electrodes 14, 16 and 18 on
7 the adjacent microprotrusions 4 are moved into the orientation shown in FIG.
8 2 by placing the plate 6 of FIG. 1 on a die (not shown) and using a punch (not
9 shown) which is pushed through the opening 8. The microprotrusions 4 of the
10 electrochemical sensor 22 are sized appropriately so that they reach through
11 the stratum corneum 24 but do not contact the patient's nerve endings 26
12 (FIG. 3). For example, the tear drop shaped electrodes 14, 16 and 18 shown
13 in FIGS. 1 and 2 at the tip of each microprotrusion 4 are about 100
14 micrometers in diameter and the microprotrusions 4 have an overall length of
15 about 150 micrometers. With this configuration, electrochemical sensor 22 is
16 responsive to changes in the presence or amount of agent in the patient's
17 interstitial fluid without causing a painful sensation or bleeding. Prior to
18 punching, the sensor 22 can be constructed using thin film mask techniques
19 utilizing thin film conductors 20 embedded or encased between layers of
20 selected insulated material such as polyimide film. The electrodes 14, 16 and
21 18 at the distal tip of each microprotrusion are inserted into the patient's skin
22 in order to contact the patient's interstitial fluid when the sensor is
23 transcutaneously placed.

24 As is known in the art and illustrated diagrammatically in FIG. 3, the
25 diamond electrodes 14, 16 and 18 are in electrical communication, through
26 conductive traces 20, with a suitable control unit 10 for detecting the patient's
27 condition (e.g., blood glucose concentration) in response to signals derived
28 from the sensor electrodes. Any suitable thin film mask techniques including
29 with reference to those disclosed in U.S. Patent Numbers 5,391,250 issued
30 February 21, 1995 to Cheney, II et al. and 5,108,819 issued April 28, 1992 to
31 Heller et al. can be used in the present invention. The sensor can be used

1 over a prolonged period of time for periodically or continuously detecting a
2 body electrolyte, such as glucose in a diabetic patient. Such readings are
3 useful in monitoring the patient's blood glucose concentration (i.e., through
4 appropriate software which correlates the concentration of glucose in
5 interstitial fluid with the concentration of glucose in the blood) and can further
6 be used to adjust a treatment regime which typically includes administration
7 of insulin to the patient and/or appropriate modification of diet and/or exercise.

8 In the illustrative sensor construction shown in FIGS. 1 and 2 designed
9 for use as a subcutaneous glucose sensor, each sensor 22 is shown to
10 include three parallel conductors or traces 20 corresponding with three
11 separate electrodes 14, 16 and 18. Appropriate electrode chemistries
12 defining the tear drop-shaped electrode surfaces at the distal ends of the
13 microprotrusions 4 can be applied as appropriate. In this illustrative sensor
14 embodiment for use as a glucose sensor, electrode 14 includes glucose
15 oxidase to define a working or sample electrode. The other two electrodes,
16 counter electrode 16 and reference electrode 18 may contain other suitable
17 chemistries, to define a counter electrode and a reference electrode for the
18 electrochemical sensor 22. As is known to those skilled in the art of
19 electrochemical analyte (e.g., glucose) sampling, at least the working
20 electrode 14 should be coated with an excluding membrane in order to limit
21 electrical interference due to oxidation or reduction of extraneous species in
22 the interstitial fluid. The excluding membrane can be comprised of two layers,
23 including a first layer for keeping scar tissue or macrophages from coating the
24 electrode and reducing the active electrode area, and a second layer for
25 excluding small molecular weight oxidizable or reducible species. In glucose
26 sensing, the second layer is typically formed of cellulose acetate and is
27 permeable to hydrogen peroxide but substantially less permeable to other
28 endogenous oxidizable/reducible species.

29 The reference electrode is typically formed of silver/silver chloride and
30 preferably contains an electrolyte having a controlled composition as is known
31 to those skilled in the electrochemical sensing arts.

1 By placing each of the electrodes 14, 16 and 18 on a separate
2 microprotrusion 4, instead of locating all of the electrodes 14, 16 and 18 on a
3 single microprotrusion 4, the electrode area is maximized while maintaining a
4 relatively small protrusion size necessary for a minimally invasive device.

5 In an alternate embodiment, the electrodes are coated onto each side
6 of the microprotrusions doubling the active electrode area. The separation of
7 electrodes on individual microprotrusions eliminates problems that are
8 associated with depositing the reference, sample and common electrodes
9 close together in a small configuration. The etched space between the
10 electrodes guarantees safe separation of the electrode coating materials so
11 that there is little chance of bleeding of one coating to another electrode
12 during manufacturing. It is within the scope of the invention, however, to
13 utilize only a single microprotrusion 4 with all of the electrodes 14, 16 and 18
14 on that one microprotrusion. Likewise, although a glucose sensor has been
15 described, any detecting system can be utilized with the device 2. It is within
16 the scope of the invention that the particular detecting system may have only
17 one or two electrodes or may have more than three electrodes. If additional
18 electrodes are needed for the detecting system, more microprotrusions can
19 be used and arranged for the best configuration. The configuration illustrated
20 in FIG. 4 utilizes multiple microprotrusions 4 around the plurality of openings 8
21 in a redundant way such that all six microprotrusions are coated with
22 electrodes. In this way, if some of the electrodes are damaged during
23 manufacturing, faulty, or do not penetrate the skin, the control unit 10 can test
24 at start up to see which electrodes are working and only utilize the working
25 electrodes for detecting the agent. Likewise, more than one set of
26 microprotrusions and openings can be located on a member 2 as shown.
27 Also, as shown in FIG. 4, two sets of three electrode sensors are shown
28 around each opening 8 for redundancy and accuracy.

29 The distal ends of microprotrusions 4 can have any of a variety of
30 shapes and configurations for piercing the skin or body surface, including
31 arrow-shaped or diamond-shaped ends as shown in FIGS. 1 and 2,

1 triangular-shaped ends as shown in FIG. 4 and pins (not shown). The
2 microprotrusions 4 penetrate the stratum corneum of the epidermis when
3 pressure is applied to the device to facilitate the detecting of an agent through
4 a body surface. The term "body surface" as used herein refers generally to
5 the outermost layer of skin, mucous membranes, and nails of an animal or
6 human, and to the outer surface of a plant.

7 In the illustrated embodiment, the plate 6 is formed with an opening 8
8 between the microprotrusions 4. The opening 8 corresponds to the portion of
9 the plate 6 occupied by each of the microprotrusions 4 prior to the
10 microprotrusions being bent into a position which is substantially
11 perpendicular to the plane of plate 6. The number of openings 8 per device
12 and the number of microprotrusions 4 per device are independent. The
13 device may have only one large opening 8 with a plurality of microprotrusions
14 4 around the opening. As will be described below, the opening 8 may be
15 covered with a fluid-attracting member for enhancing the movement of an
16 agent being sampled past the electrodes and into a fluid-attracting reservoir.
17 In another embodiment, the device does not have an opening 8 through the
18 plate 6. In this latter embodiment, the microprotrusions 4 are made by
19 molding or casting and are then coated with the electrodes.

20 The microprotrusions 4 are generally formed from a single piece of
21 material (although they need not be) and are sufficiently sharp and long for
22 puncturing at least the stratum corneum of the body surface. In one
23 embodiment, the microprotrusions 4 and the plate 6 are essentially
24 impermeable or are impermeable to the passage of an agent. The width of
25 each microprotrusion can be any of a range of widths. Usually, the width of
26 the microprotrusion is in the range of about 25 micrometers to 500
27 micrometers. The length of the microprotrusions is subject to variation of the
28 body surface being penetrated and corresponds to the natural thickness of
29 the stratum corneum for one of the features of the invention is that the sensor
30 electrode detects the agent below the outermost layer of the epidermis.
31 Usually, the microprotrusions will be about 20 micrometers to about 400

1 micrometers in length. The microprotrusions 4 can have slanted (i.e., angled)
2 leading edges 64 (FIG. 4) to further reduce the insertion force required to
3 press the microprotrusions into the body surface. The leading edges of each
4 microprotrusion can be all the same angle or can be at different angles
5 suitable for piercing the body surface. Alternatively, the leading edge of each
6 microprotrusion can be arcuate (i.e., curved) in shape, having, for example, a
7 convex or concave shape.

8 The member 2 can also improve the attachment of the device to the
9 body surface so that continuous agent detection through the body surface is
10 preserved during movement of the body surface. In the embodiment shown
11 in FIG. 4, projections in the form of barbs 50 on at least one of the
12 microprotrusions 4 assist in anchoring the member 2 and any corresponding
13 device or structure used in combination therewith to the body surface. Barbs
14 50 can be on any number of the microprotrusions from one to all
15 microprotrusions. The barbs 50 are optional as other means for holding the
16 member in contact with the body surface can be used. The present invention
17 can be used in conjunction with a wide variety of microprotrusions
18 configurations, for example, reference may be had to U.S. Provisional
19 Application No. 60/019,990 filed June 18, 1996 of which any of the disclosed
20 configurations can be used with the present invention.

21 The pattern for any of the microprotrusion array members 2 of the
22 present invention can be produced with a photo-etching process. For
23 example, reference may be had to U.S. Provisional Application No.
24 60/019,990 filed June 18, 1996 of which any of the disclosed methods can be
25 used to produce the member 2 of the present invention. A thin plate 6 of
26 metal such as stainless steel or titanium is etched photo-lithographically with
27 patterns containing skin piercing structures. In general, a thin laminate dry
28 resist or wet resist is applied on the plate 6 which typically has a thickness of
29 about 7 micrometers to about 100 micrometers, preferably about 25
30 micrometers to about 50 micrometers. The resist is contact exposed using a
31 mask having the desired pattern and is subsequently developed. These

1 operations are conducted in much the same way that they are for the
2 manufacture of a printed circuit board. The plate 6 is then etched using acidic
3 solutions. After the pattern has been etched through the plate, the plate 6 is
4 placed on a die having a plurality of openings corresponding to the openings
5 8 in the plate. A punch having a plurality of protrusions corresponding to the
6 openings 8 in the plate 6 and openings in the die is initially located above the
7 plate and the die. At the initial stage, the microprotrusions 4 are in the same
8 plane as the rest of the plate 6. The punch dies are then pressed into the
9 openings 8, thus bending the microprotrusions downward to be substantially
10 perpendicular to the plane of the plate 6. The finished structure provides
11 microprotrusions 4 with an adjacent opening 8. In one embodiment, the
12 opening 8 allows the passage of interstitial fluid therethrough when the
13 member 2 is applied to the body surface. Rectangular openings 8 are shown
14 in the figures but the invention encompasses the use of any shape openings
15 including, but not limited to, square, triangular, circular and elliptical.

16 Generally, the microprotrusions 4 are at an angle of about 90 degrees
17 to the surface 48 (FIG. 3) of the plate 6 after being punched, but they can be
18 disposed at any angle forward or backward from the perpendicular position
19 that will facilitate penetration of and attachment to the body surface. In
20 addition, other anchoring elements such as barbs, openings, etc. can be used
21 with the angled microprotrusions to further enhance anchoring of the device.

22 The plates 6 and microprotrusions 4 can be made from materials that
23 have sufficient strength and manufacturability to produce microprotrusions,
24 such as, glasses, ceramics, rigid polymers, metals and metal alloys.

25 Examples of metals and metal alloys include but are not limited to stainless
26 steel, iron, steel, tin, zinc, copper, silver, platinum, aluminum, germanium,
27 nickel, zirconium, titanium and titanium alloys having nickel, molybdenum or
28 chromium. Each of the plate and microprotrusions can have a thin layer of
29 silver, gold, platinum, iridium, titanium, rhodium plating or evaporated or
30 sputtered biocompatible metals to provide for inertness, biocompatibility and
31 preservation of the sharpness of the edges during storage. An example of

1 glasses include a devitrified glass such as "PHOTOCERAM" available from
2 Corning in Corning, NY. Examples of polymers include but are not limited to
3 polystyrene, polymethylmethacrylate, polypropylene, "BAKELITE", cellulose
4 acetate, ethyl cellulose, styrene/acrylonitrile copolymers, styrene/butadiene
5 copolymers, acrylonitrile/butadiene/styrene (ABS) copolymers, polyvinyl
6 chloride and acrylic acid polymers including polyacrylates and
7 polymethacrylates.

8 The number of microprotrusions 4 and electrodes of any of the
9 embodiments of the member 2 is variable with respect to the redundancy
10 desired in the system, the agent being detected, the type of sensor being
11 used, and other factors as will be evident to one of ordinary skill in the art.

12 The member 2 can optionally be made to adhere to the patient's body
13 surface by various means, including an adhesive applied to the body-
14 contacting side of plate 6 or other anchoring elements on the member 2 of
15 any of the embodiments discussed herein. Further, a watch band or elastic
16 bandage can be used to maintain the device in contact with the skin. The
17 adhesive should have sufficient tack to insure that the member 2 remains in
18 place on the body surface during normal user activity, and yet permits
19 reasonable removal after the predetermined (e.g., 24-hour) wear period. A
20 suitable release liner (not shown) is preferably provided for maintaining the
21 integrity of the adhesive before use. In use, the release liner is stripped from
22 the adhesive before the device is applied to the skin.

23 As mentioned, the member 2 of the present invention can also be used
24 with fluid-attracting regimes including, but not limited to, reverse
25 electrotransport (i.e., iontophoresis and/or electroosmosis), osmosis, and
26 passive diffusion. Figure 5 illustrates an osmotic device 104 in combination
27 with any of the embodiments described previously for member 2. Osmotic
28 devices can be used to draw fluid from the body (i.e., interstitial fluid or sweat)
29 which carries the agent to be detected, for example, reference may be had to
30 U.S. Patent No. 4,756,314 of which the disclosed osmotic configurations can
31 be used with the present invention. The osmotic device 104 is attached to a

1 body surface by means of a flexible adhesive overlay 100. Device 104 is
2 comprised of a salt layer 106 separated by semi-permeable membrane 95
3 from control unit or detector 10 and member 2. The salt layer 106 draws fluid
4 from the patient's body by osmosis. The fluid drawn from the body contains
5 the agent being detected. In this way, with the electrodes located at the distal
6 ends of the microprotrusions, a constant flow of interstitial fluid can be
7 maintained past the electrodes and through the openings 8. Preferably, the
8 salt layer 106 is free to expand or is encapsulated in a semi-permeable
9 membrane 95 so that it retains the fluid therein. With this configuration, the
10 agent is detected in situ below the body surface as the interstitial fluid flows
11 past the electrodes. Alternatively, salt layer 106 and semi-permeable
12 membrane 95 can be combined in one layer of absorbent hydrogel that stores
13 the absorbed fluid as well as the agent.

14 It will be appreciated by those of ordinary skill in the art that the
15 invention can be embodied in other specific forms without departing from the
16 spirit or essential character thereof. The presently disclosed embodiments
17 are therefore considered in all respects to be illustrative and not restrictive.
18 The scope of the invention is indicated by the appended claims rather than
19 the foregoing description, and all changes which come within the meaning
20 and range of equivalents thereof are intended to be embraced therein.

1 CLAIMS:

2

3 1. A detecting device, comprising a plate (6) having at least one
4 microprotrusion (4) extending therefrom, characterized in that,
5 a sensor (22) is on the microprotrusion (4) to detect an agent below the
6 outermost layer (24) of a body surface.

7

8 2. The detecting device of Claim 1 characterized in that the device further
9 comprises:

10 a detector (10) and wherein the sensor (22) is an electrochemical
11 sensor having a proximal segment attached to the detector (10) and a distal
12 segment having at least one electrode (14, 16, or 18) thereon.

13

14 3. The detecting device as claimed in Claim 1 characterized in that the
15 microprotrusion (4) locates the sensor (22) just below the outermost layer of
16 the epidermis above the nerve endings (26) and blood vessels of a patient.

17

18 4. The detecting device as claimed in Claim 1 characterized in that the
19 sensor (22) is a thin film sensor.

20

21 5. The detecting device as claimed in Claim 1 characterized in that the
22 sensor (22) is a glucose sensor.

23

24 6. The detecting device as claimed in Claim 1 characterized in that the
25 sensor (22) is located on two sides of the microprotrusion (4).

26

27 7. The detecting device as claimed in Claim 1 characterized in that the
28 microprotrusion (4) further comprises means (50) for anchoring the device (2)
29 in the body surface.

30

31 8. The detecting device as claimed in Claim 1 characterized in that the
32 plate (6) has an opening (8) therethrough in communication with a fluid-
33 attracting member (106).

34

35 9. The detecting device as claimed in Claim 8 characterized in that the
36 fluid-attracting member (106) is an osmotic salt layer.

37

1 10. A device for detecting an agent below the outermost layer (24) of the
2 epidermis of a patient, comprising:

3 at least one electrochemical sensor (22); and

4 a plurality of skin-piercing microprotrusions (4), each of the skin-
5 piercing microprotrusions (4) having an electrode (14, 16, or 18) of the
6 electrochemical sensor (22) thereon.

7

8 11. The device as claimed in Claim 10 characterized in that the skin-
9 piercing microprotrusions (4) locate the sensor (22) just below the outermost
10 layer (24) of the epidermis above the nerve endings (26) and blood vessels of
11 the patient.

12

13 12. The device as claimed in Claim 10 characterized in that one of the
14 skin-piercing microprotrusions (4) is a sample electrode (14) , one of the skin-
15 piercing microprotrusions (4) is a common electrode (16), and one of the skin-
16 piercing microprotrusions is a reference electrode (18).

17

18 13. The device as claimed in Claim 10, further comprising electrical traces
19 (20) extending from each of the electrodes (14, 16 and 18) to interface with a
20 detector (10).

21

22 14. The device of as claimed in Claim 10 characterized in that each skin-
23 piercing microprotrusion (4) has an enlarged electrode surface at its distal
24 end.

25

26 15. The device as claimed in Claim 10 characterized in that each skin-
27 piercing microprotrusion (4) has a diamond-shaped electrode surface at its
28 distal end.

29

30 16. The device as claimed in Claim 10 characterized in that the device has
31 an opening (8) therethrough in communication with a fluid-attracting member
32 (106).

33

34 17. The device as claimed in Claim 16 characterized in that the fluid-
35 attracting member (106) is an osmotic salt layer.

36

- 1 18. The device as claimed in Claim 10 characterized in that the electrode
2 (14, 16, or 18) of each of the skin-piercing microprotrusions (4) is located on
3 two sides of the microprotrusion (4).
4
- 5 19. The device as claimed in Claim 10 characterized in that the
6 electrochemical sensor (22) is a glucose sensor.
7
- 8 20. A method for detecting an agent through a patient's skin, characterized
9 by the steps of:
10 piercing the patient's skin with at least one microprotrusion (4)
11 extending from a detecting device (2, 10), the microprotrusion (4) having a
12 sensor (22) thereon to detect an agent below the outermost layer (24) of the
13 epidermis of the patient; and
14 detecting the presence of the agent.
15
- 16 21. The method as claimed in Claim 20 further comprising:
17 locating the sensor (22) just below the outermost layer (24) of the
18 epidermis above the nerve endings (26) and blood vessels of the patient.
19
- 20 22. The method as claimed in Claim 20 further comprising:
21 withdrawing fluid from the patient's skin with the detecting
22 device (2, 10) to produce a flow of fluid past the sensor (22).
23
- 24 23. The method as claimed in Claim 20 characterized in that the detecting
25 step is performed periodically.

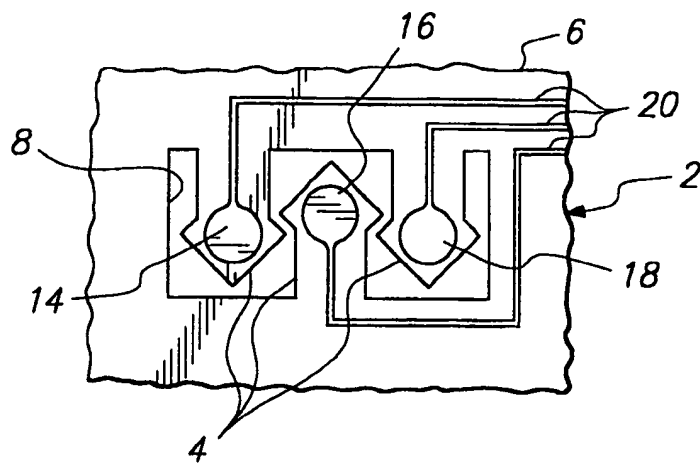


FIG. 1

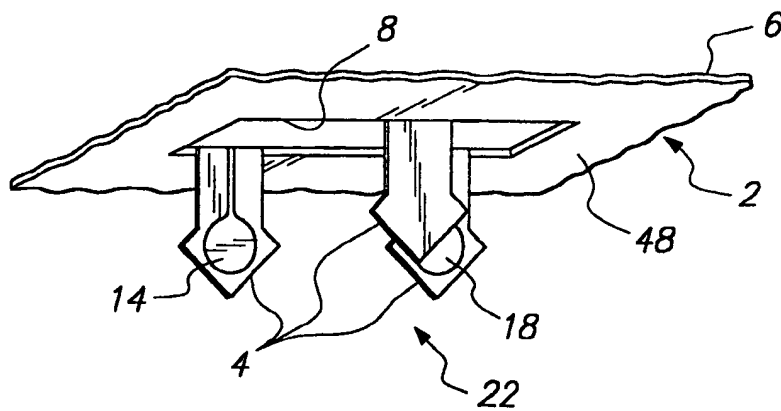
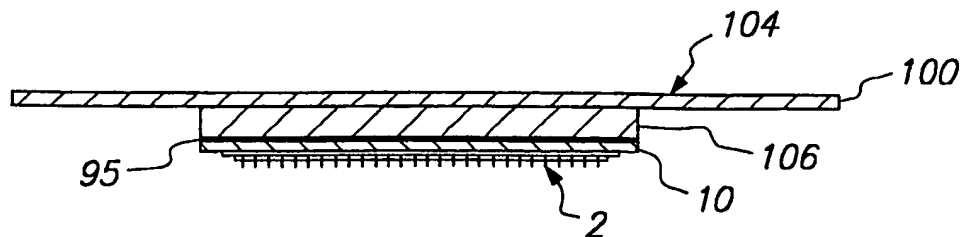
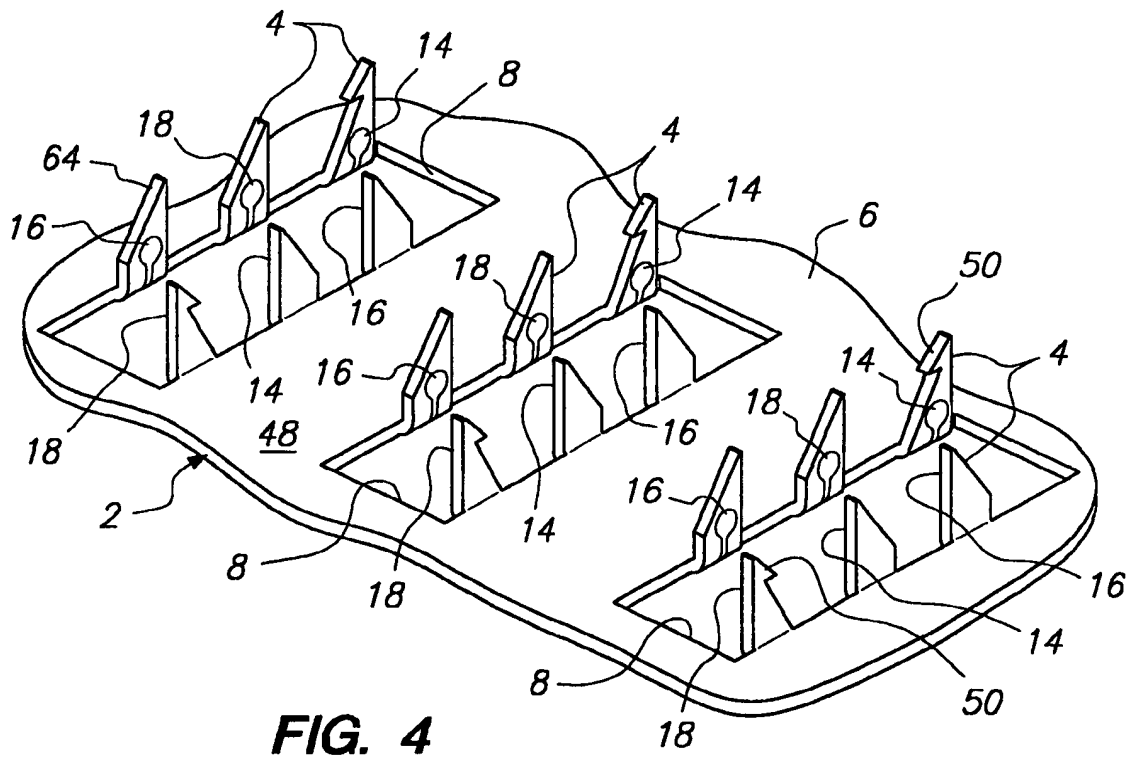
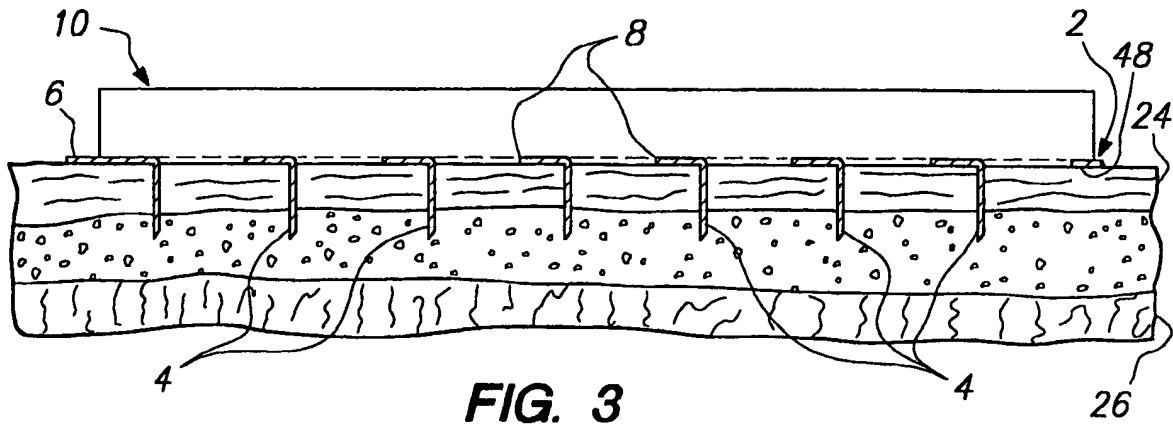


FIG. 2



INTERNATIONAL SEARCH REPORT

national Application No

PCT/US 98/06851

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61B5/00

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

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